

# **Burden of hepatitis E virus infection in pregnancy and maternofetal outcomes: a systematic review and meta-analysis**

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Supplementary Table 1. Search strategy in PubMed

<b>Search</b>	<b>Search terms</b>
#1	"hepatitis E" OR "viral hepatitis E" OR "hepatitis E virus" OR "hepatitis E antibody" OR "hepatitis E antigen"
#2	"hepatitis non A non B" OR "hepatitis non A non B non C" OR "hepatitis virus non A non B"
#3	#1 OR #2
#4	"pregnancy" OR "pregnant women" OR "antenatal" OR pregnan* OR "prenatal" OR gravidity OR parturition OR maternal
#5	Fetal OR foetal OR fetomaternal OR maternofetal OR maternofetal OR foeto-maternal OR fetus
#6	#4 OR #5
#7	#3 AND #6

Supplementary Table 2 : Risk of bias tool

Risk of Bias Item	Yes (Low Risk) or No (High risk)
<b>External Validity</b>	
1. Was the study target population a close representation of the pregnant population in relation to relevant variables?	
2. Was the sampling frame a true or close representation of the target population?	
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	
4. Was the likelihood of non-participation bias minimal?	
<b>Internal Validity</b>	
5. Were data collected directly from the subjects (as opposed to medical records)?	
6. Were acceptable case definition of HEV used?	
7. Was a reliable and accepted diagnosis method for HEV utilised?	
8. Was the same mode of data collection used for all subjects?	
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	
10. Were the numerator(s) and denominator(s) for the calculation of the prevalence of dyslipidemia appropriate?	
<p>11. Summary item on the overall risk of study bias</p> <p>LOW RISK OF BIAS: 8 or more “yes” answers. Further research is very unlikely to change our confidence in the estimate.</p> <p>MODERATE RISK OF BIAS: 6 to 7 “yes” answers. Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.</p>	

HIGH RISK OF BIAS: 5 or fewer “yes” answers. Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.	
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Supplementary Table 3 : Risk of bias on study investigating the association between HEV infection and maternofetal outcomes

Author	Year	Is there potential for confounding of the effect of HEV in this study?	Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Bias due to confounding	Was selection of participants into the study (or into the analysis) different between women with HEV and women without HEV?	Bias in selection	Were exposure/non exposure groups clearly defined?	Could classification of HEV exposure or not exposure status have been affected by knowledge of the outcome or risk of the outcome?	Bias in classification of exposure	Were outcome data available for all, or nearly all, participants?	Were participants excluded due to missing data on other variables needed for the analysis?	Bias due to missing data	Could the outcome measure have been influenced by knowledge of the exposure received?	Were outcome assessors aware of the HEV exposure by study participants?	Were the methods of outcome assessment comparable across HEV positive and HEV negative groups?	Bias in Outcome Measurement	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the exposure-outcome relationship?	Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Bias in selection of report domain	Global
Kumar	2014	Probably No	No	Moderate	No	Low	Yes	No	Low	Yes	No	Low	No	No Information	Yes	Moderate	No	No	No	Low	Moderate
Devi	2014	Probably No	No	Moderate	No	Low	Yes	No	Low	Yes	No	Low	No	No Information	Yes	Moderate	No	No	No	Low	Moderate
Bhatnagar	2016	Probably No	No	Moderate	No	Low	Yes	No	Low	Yes	No	Low	No	No Information	Yes	Moderate	No	No	No	Low	Moderate
Javed	2017	Probably No	No	Moderate	No	Low	Yes	No	Low	Yes	No	Low	No	No Information	Yes	Moderate	No	No	No	Low	Moderate
Patra	2007	Probably No	No	Moderate	No	Low	Yes	No	Low	Yes	No	Low	No	No Information	Yes	Moderate	No	No	No	Low	Moderate

Supplementary Table 4 : Individual characteristics of studies included in the meta-analysis prevalence of HEV infection in the global population of pregnant women

Author	Year	Sample	Clinical presentation	Risk of bias	Country	Period	Design	Number of centers	Area	Setting	Timing	Sampling	Age, y	%HAV	%HBV	%HCV	%HDV	%Nulliparous
Abebe	2017	386	None	Low	Ethiopia	2014-2015	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	28.9	NR	NR	NR	NR	NR
Adjei	2009	157	None	Moderate	Ghana	2008	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	28.89	NR	NR	NR	NR	NR
Ahmed	2008	60	AVH	Moderate	Sudan	2007	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	26.8	NR	31.30%	6.30%	NR	NR
Banait	2007	156	Liver dysfunction	Moderate	India	2003-2004	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Retrospective	Unclear/not described	25.5	NR	1.30%	NR	NR	28.6
Beniwal	2003	97	Liver dysfunction	Moderate	India	2000-2002	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	NR	5.20%	7.20%	0	NR	0
Bhatia	2008	249	AVH	Moderate	India	1986-2006	Cross-sectional	Multi-center	Unclear/not described	Other hospital based (not antenatal care)	Retrospective	Consecutive	25.6	1.20%	4.80%	NR	NR	NR
Bista	2006	19	Jaundice	High	Nepal	1999-2003	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Retrospective	Unclear/not described	24	NR	NR	NR	NR	62.5
Borkakoti	2013	585	AVH and ALF	Moderate	India	2006-2011	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	24.6	1.40%	2.40%	8.20%	NR	NR
Brohi	2013	52	FHF	Moderate	Pakistan	2009-2010	Cross-sectional	Single-center	Urban, Rural	Other hospital based (not antenatal care)	Prospective	Unclear/not described	29.04	NR	17.30%	13.50%	NR	NR
Cevrioglu	2004	245	None	Moderate	Turkey	2000-2002	Cross-sectional	Multi-center	Urban, Rural	Other hospital based (not antenatal care)	Prospective	Unclear/not described	26.3	NR	NR	NR	NR	NR
Changede	2018	43	Jaundice	Moderate	India	2016	Cross-sectional	Single-center	Urban, Rural	Other hospital based (not antenatal care)	Retrospective	Unclear/not described	NR	2.30%	4.60%	NR	NR	51
Cong	2015	990	None	Moderate	China	2011-2013	Cross-sectional	Multi-center	Urban, Rural	Antenatal care, Other hospital based (not antenatal care)	Prospective	Consecutive	NR	NR	NR	NR	NR	NR
Cordova	2007	20	None	Moderate	Brazil	2004	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	NR	NR	NR	NR	NR	NR
De Paschale	2016	278	None	Moderate	Benin	2011	Cross-sectional	Single-center	Rural	Other hospital based (not antenatal care)	Retrospective	Unclear/not described	26.2	0	NR	NR	NR	19
Devi	2014	262	AVH	Moderate	India	NR	Cross-sectional	Multi-center	Unclear/not described	Antenatal care, Other hospital based (not antenatal care)	Prospective	Unclear/not described	NR	NR	NR	NR	NR	NR
Elduma	2014	39	Fever	Moderate	Sudan	2012	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	26	NR	NR	NR	NR	NR
Farshadpour	2018	1331	None	Low	Iran	2016-2017	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care), Population/Community-based study	Prospective	Consecutive	27.93	NR	NR	NR	NR	5.1
Hamid	1996	12	AVH	Moderate	Pakistan	1991-1994	Cross-sectional	Unclear/not described	Urban	Unclear/not described	Prospective	Unclear/not described	25	8.30%	16.70%	0	NR	25
Hannachi	2011	404	None	Low	Tunisia	2006	Cross-sectional	Single-center	Urban, Rural	Antenatal care	Prospective	Consecutive	30.08	10%	0.03	0.50%	NR	NR

Huang	2015	274	None	High	China	2015	Cross-sectional	Single-center	Urban	Population/Community-based study	Prospective	Unclear/not described	NR	NR	NR	NR	NR	NR
Huang	2013	293	None	Moderate	China	NR	Cross-sectional	Single-center	Urban	Unclear/not described	Prospective	Unclear/not described	27.9	NR	NR	NR	NR	NR
Jaiswal	2001	127	AVH and FHF	Moderate	India	1992_1999	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	NR	0	18.89%	0	0.78%	NR
Javed	2017	135	Jaundice or abnormal liver function	Moderate	Pakistan	2015	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	29.2	NR	5.20%	5.20%	NR	15
Jilani	2007	50	FHF	Moderate	India	NR	Cross-sectional	Multi-center	Unclear/not described	Other hospital based (not antenatal care)	Prospective	Unclear/not described	24.8	0.02	0	0	NR	NR
Junaid	2014	108	None	Moderate	Nigeria	NR	Cross-sectional	Single-center	Urban, Rural	Population/Community-based study	Prospective	Non-probability	NR	NR	NR	NR	NR	NR
Kar	2008	125	Jaundice	Low	India	NR	Cross-sectional	Multi-center	Urban	Antenatal care, Other hospital based (not antenatal care)	Prospective	Consecutive	24.8	12%	0.08	0.02	NR	NR
Khuroo	2003	49	ALF	Low	India	1989-1996	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	31.1	2.20%	13.90%	7.20%	1.10%	NR
Khuroo	2003	76	AVH	Low	India	1993-1996	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Systematic	27.7	1.50%	0.15	1.70%	1.50%	NR
Kumar	2004	62	Jaundice	Moderate	India	2001-2002	Cross-sectional	Unclear/not described	Unclear/not described	Antenatal care, Other hospital based (not antenatal care)	Prospective	Consecutive	24.5	0	4.80%	0	NR	NR
Kumar	2011	24	None	Moderate	India	2002-2006	Cross-sectional	Single-center	Urban	Unclear/not described	Retrospective	Unclear/not described	NR	0	8.30%	0	NR	NR
Kumar	2017	256	Jaundice	Moderate	India	2011-2014	Cross-sectional	Multi-center	Urban	Antenatal care, Other hospital based (not antenatal care)	Prospective	Consecutive	24.6	0.07%	3.40%	3.40%	NR	0
Kumar	2007	24	Jaundice	High	India	2002-2006	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	NR	14.60%	12.20%	3.60%	NR	NR
Kumar	2017	177	Jaundice	Moderate	India	2016	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Retrospective	Unclear/not described	25	0.40%	30.50%	8.40%	NR	NR
Kumar	2001	469	None	Low	United Arab Emirates	NR	Cross-sectional	Single-center	Urban	Antenatal care	Prospective	Consecutive	25	NR	NR	NR	NR	NR
Lindemann	2010	1040	None	Moderate	Spain	2007-2010	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	30.6	NR	NR	NR	NR	NR
Mahtab	2009	31	AVH	Moderate	Bangladesh	2004-2006	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Retrospective	Consecutive	NR	4.86%	27.80%	NR	NR	NR
Neffati	2017	216	None	Low	Tunisia	2014-2015	Cross-sectional	Multi-center	Urban	Antenatal care	Prospective	Consecutive	32	9.80%	NR	NR	NR	NR
Obiri-Yeboah	2018	398	None	Moderate	Ghana	NR	Cross-sectional	Multi-center	Urban, Rural	Antenatal care	Prospective	Systematic	28.01	NR	NR	NR	NR	NR
Oncu	2006	386	None	Moderate	Turkey	NR	Cross-sectional	Multi-center	Urban, Rural	Other hospital based (not antenatal care)	Prospective	Multistage sampling	24.28	NR	NR	NR	NR	NR
Patra	2007	220	Jaundice	Low	India	2003-2005	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	22.4	NR	NR	NR	NR	NR
Pujol	1994	184	None	Moderate	Venezuela	1991-1992	Cross-sectional	Multi-center	Urban, Rural	Other hospital based (not antenatal care)	Prospective	Unclear/not described	NR	NR	NR	NR	NR	NR

Rathi	2007	107	Liver dysfunction	Moderate	India	2002-2004	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	NR	NR	4.20%	4.20%	NR	NR
Renou	2014	315	None	Moderate	France	NR	Cross-sectional	Multi-center	Unclear/not described	Other hospital based (not antenatal care)	Prospective	Unclear/not described	NR	NR	NR	NR	NR	NR
Sahai	2015	68	AVL	Moderate	India	2007-2009	Cross-sectional	Unclear/not described	Unclear/not described	Unclear/not described	Prospective	Consecutive	NR	0	7.40%	1.50%	NR	NR
Salam	2013	272	Jaundice	High	India	2008-2011	Cross-sectional	Multi-center	Unclear/not described	Antenatal care	Prospective	Unclear/not described	24.76	1.80%	8.80%	2.70%	NR	NR
Singh	2003	60	AVH	Moderate	India	1997-1998	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	24	0	0.1	0	NR	NR
Solanke	2016	103	Liver dysfunction	Moderate	India	2013-2015	Cross-sectional	Unclear/not described	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	25	NR	NR	NR	NR	NR
Strand	2003	60	Both	Moderate	Angola	1999	Case-control (group of pregnant women)	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	Consecutive	21.9	NR	0.1	0	NR	55
Sultana	2014	38	Jaundice	Moderate	Pakistan	2012-2013	Cross-sectional	Single-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	25	12%	NR	NR	NR	40
Surya	2005	819	None	Moderate	Indonesia	2003	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	Unclear/not described	27	NR	1.90%	0.04%	NR	NR

NR: not reported; AVH: acute viral hepatitis, FHF: fulminant hepatitis failure; ALF: acute liver failure



Supplementary Table 5 : Individual characteristics of studies included in the meta-analysis of pregnancy outcomes in HEV infection in the global population of pregnant women

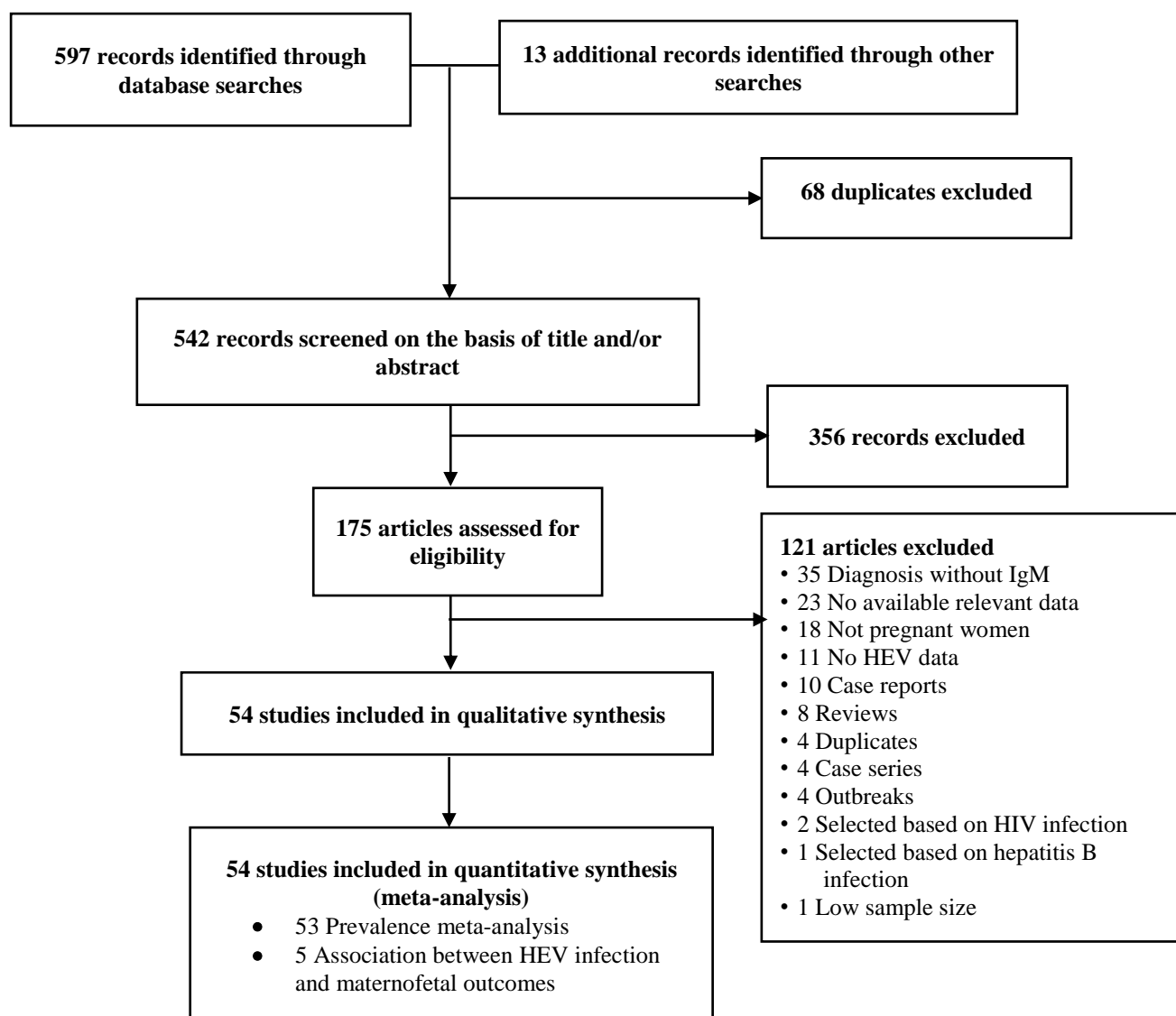
Author	Year of publication	Country	Design	Number of centers	Area	Setting	Timing of data collection	Period	Sampling	Age HEV+	Age HEV -	%HAV in HEV+	%HAV in HEV-	%HBV in HEV+	%HBV in HEV-	%HCV in HEV+	%HCV in HEV-	%HDV in HEV+	%HDV in HEV-	%HIV in HEV+	%HIV in HEV-	%Nulliparous in HEV+	%Nulliparous in HEV-	
<b>Patra</b>	2007	India	Cross-sectional	Multi-center	Urban	Other hospital based (not antenatal care)	Prospective	2003-2005	Consecutive	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
<b>Kumar</b>	2014	India	Cross-sectional	Multi-center	Unclear/not described	Antenatal care, Other hospital based (not antenatal care)	Unclear/not described	NR	Unclear/not described	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
<b>Devi</b>	2014	India	Cross-sectional	Multi-center	Unclear/not described	Antenatal care, Other hospital based (not antenatal care)	Unclear/not described	NR	Unclear/not described	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
<b>Bhatnagar</b>	2016	India	Cross-sectional	Multi-center	Urban	Antenatal care, Other hospital based (not antenatal care)	Prospective	2012-2014	Consecutive	24.10	25.57	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
<b>Javed</b>	2017	Pakistan	Cross-sectional	Multi-center	Unclear/not described	Unclear/not described	Prospective	2015	Unclear/not described	29.2	28.6	NR	NR	2.2%	3.0%	0.7%	4.4%	NR	NR	NR	NR	NR	NR	NR

NR: Not reported

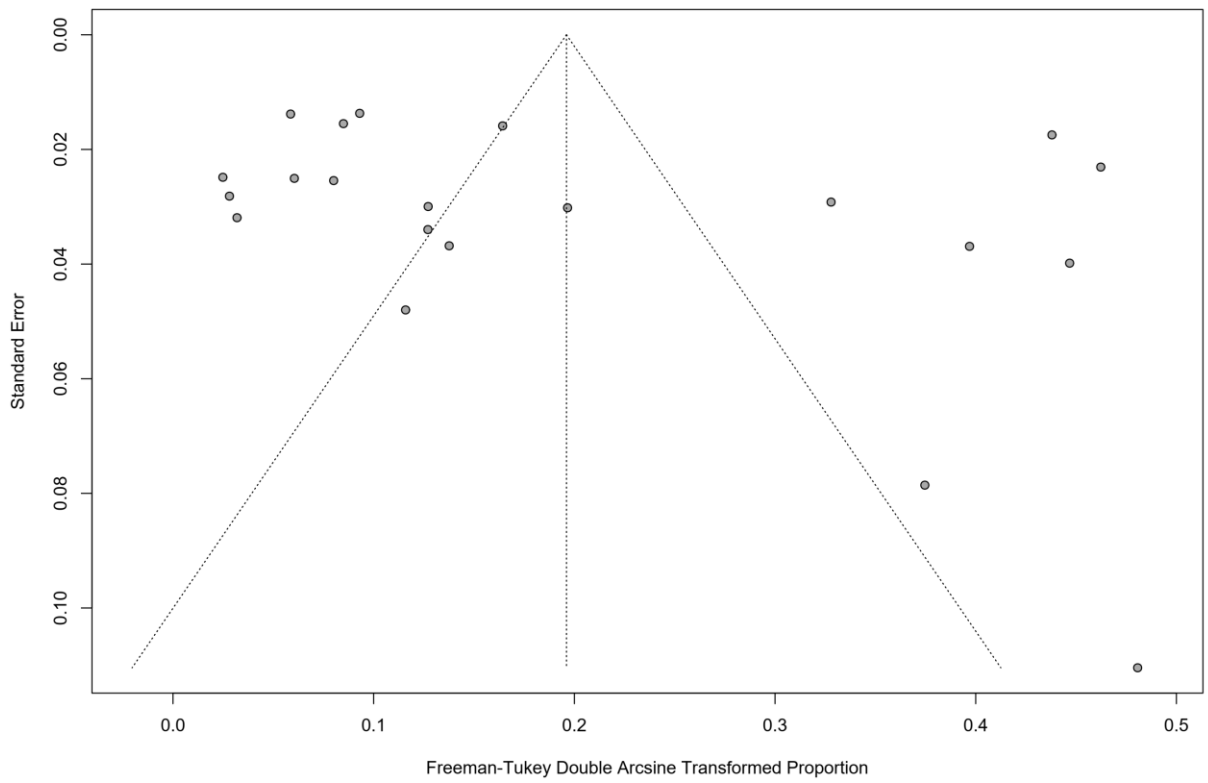
Supplementary Table 6 : *Characteristics of studies included in the meta-analysis*

<b>Characteristics</b>	<b>N = 54</b>
Year of publication, range	1994-2018
Period of recruitment, range	1986-2017 (n = 42)
% of Nulliparous	0 – 62.5 (n = 11)
<b>Clinical profile</b>	
- Asymptomatic	24
- Symptomatic	29
- Both	1
<b>WHO Regions</b>	
- South-East Asia	25
- Eastern Mediterranean	10
- Africa	7
- Europe	4
- Americas	3
- Western Pacific	3
<b>Design</b>	
- Cross sectional	53
- Case control	1
<b>Setting</b>	
- Antenatal care	14
- Hospital-based	34
- Population-based	2
- Unclear	4
<b>Timing of data collection</b>	
- Prospective	45
- Retrospective	9
<b>Sampling method</b>	
- Consecutive	25
- Multistage random	1
- Random sampling	1
- Systematic	2
- Unclear	25

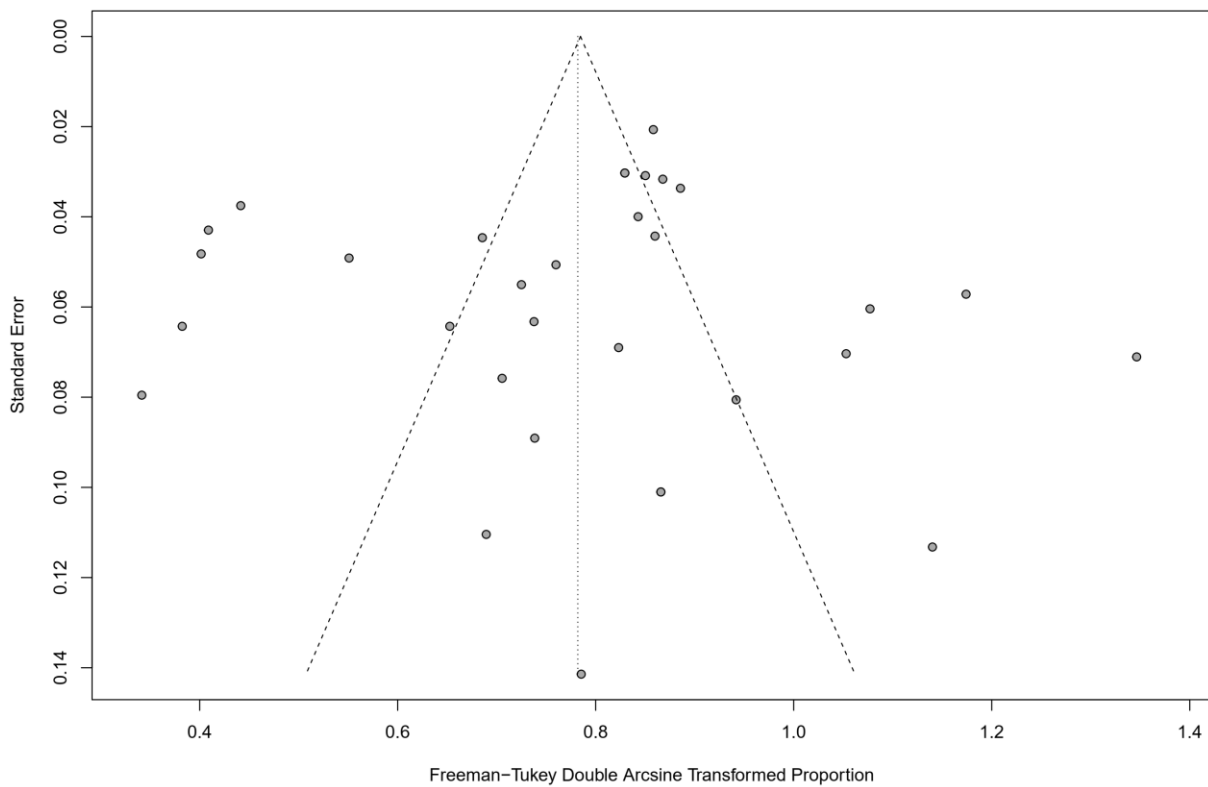
Supplementary Figure 1 : *The review process*



Supplementary Figure 2 : Funnel plot for HEV prevalence in asymptomatic pregnant women



Supplementary Figure 3 : Funnel plot for HEV prevalence in symptomatic pregnant women



## List of included studies<sup>[1-54]</sup>

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